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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,373	MEDOF ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-15,19 and 20* is/are pending in the application.

4a) Of the above claim(s) *8-11 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7,12,14,15,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 5, 7-15, 19 and 20 are pending.

Claims 8-11 and 13 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions. Claim 34 is withdrawn from examination because the elected differentiation antigen in claim 33 is not a tumor antigen.

Claims 1-2, 5, 7, 12, 14-15, 19 and 20, drawn to a protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, a polypeptide providing a functional unit of a second complement regulatory protein, a protein having at least 95 percent sequence homology to a protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ IDNO: 19 and SEQ ID NO: 23 and a method of regulating complement activity comprising administering an effective amount of said protein, are being acted upon in this Office Action.

Objection and Rejections Withdrawn

The objection to claim 7 because of typographical error and missing punctuation mark is withdrawn in view of the claim amendment filed December 6, 2010.

The rejection of claims 1-2 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment filed December 6, 2010.

The rejection of claims 1, 3, 4, 14 and under 35 U.S.C. 102(b) as being anticipated by WO 95/08570 publication (published March 30, 1995; PTO 892) is withdrawn in view of the claim amendment filed December 6, 2010. Specifically, the WO 95/08570 publication does not teach the second functional units from CCPs 8-10 of Complement Receptor 1 (CR1) or CCPs 15-17 of CR1 or polypeptides derived from Fc fragments of IgG4 or lipid tail.

The rejection of claims 1, 2 and 4 under 35 U.S.C. 103(a) as being unpatentable over WO 95/08570 publication (published March 30, 1995; PTO 892) in view of Harris et al (J Biol Chemistry 278(38): 36068-36076, September 2003; PTO 892) as evidenced by Smith et al (J Immunol 154: 2226-2236, 1995; PTO 892) is withdrawn in view of the claim amendment filed December 6, 2010.

Rejection Remains

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 7 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claims 5 and 7 is indefinite because the metes and bounds of what would constitute a "substantially all" cannot be determined. Such is a relative term, and neither the specification nor the claims provide adequate guidance to the interpretation of such term.

Applicants' arguments filed December 6, 2010 have been fully considered but are not found persuasive.

Applicants' position is that here, the term "substantially" is used to modify the terms "all of the amino acids of CCPs 11-14 of CR1" and "all of the amino acids of CCPs 4-7 of CR1 in claims 5 and "all of the amino acids of CCPs 4-5 of CR1" in claim 7. The specification specifically states: "As used herein the term substantially all means that the spacer may lack a few, e.g., 1-10 amino acids from the N terminus and/or the C terminus of the spacer." see [0060]. Therefore, Applicants respectfully put forth that in light of the specification, one of ordinary skill in the art would understand that the phrase substantially all of the amino acids recited in claims 5 and 7 would clearly indicate that a spacer may lack 1-10 amino acids from the N terminus and/or the C terminus of the spacer.

In response, a closer inspection of the specification paragraph [0060] reveals that "In one preferred embodiment, the spacer comprises all or substantially all of CCPs 4-7 of CR1, **i.e.,** amino acid 239 through amino acid 496 of the CR1 sequence shown in Fig.2 (SEQ. ID NO: 3). In another preferred embodiment the spacer comprises all or substantially all of CCPs 11-14 of the CR1 protein. As used herein the term substantially all means that the spacer may lack a few, **e.g**. 1-10 amino acids from the N terminus and/or the C terminus of the spacer. The spacer may also comprise some amino acids that result from incorporating a restriction enzyme site into the spacer. Thus, the spacer may comprise a few amino acids at the N terminus or C terminus that are different from the amino acids that are found at the N terminus or C terminus of the CCP4-7 fragment that is derived from native CR1 or the CCP 1-14 fragment that is derived from native CR1. The spaced may also contain substitutions within a sequence as described above, such that the spacer has at least about 95 percent homology to a corresponding native sequence.

The terms "i.e.," and "e.g." are open-ended language and are not limited to a spacer that may lack 1-10 amino acids from the N terminus and/or the C terminus of the spacer as argued. As such, the mete and bound of what would constitute a "substantially all" cannot be determined.

Claim rejections under - 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

Claims 1-2, 5, 7, 12, 14-15, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a protein comprising the amino acid sequence that is at least 95% identical to a protein selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23 and (2) a method of inhibiting complement activity comprising administering an effective amount of a protein to a human, rat or mouse subject wherein the protein comprises the sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23, **does not** reasonably provide enablement for any protein as set forth in claims 1-2, 5, 7, 12, 14-15, 19 and 20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompass a genus of protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating

properties; any first spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, attached to the first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1) from any species, any CCPs 15-17 of CR1, any polypeptides derived from any Fc fragment of any IgG4 and a lipid tail.

Enablement is not commensurate in scope with how to make and use any protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of DAF from any species; a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of any Complement Receptor 1 (CR1), CCPs 15-17 of any CR1, any polypeptides derived from Fc fragments of IgG4.

At the time of filing, the specification discloses just human DAF (CD55) and human CR1 (CD35). The specification discloses chimeric protein comprising a first functional unit of a first complement regulatory protein, wherein the first functional unit consisting of CCPs 2-4 of human DAF, a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of human Complement Receptor 1 (CR1), CCPs 15-17 of human CR1, the Fc fragment of IgG4 wherein the Fc fragment consisting of a hinge, CH2 and CH3 domain, and a lipid tail.

The term “comprises" is open ended. It extends the DAF functional unit to include the full-length sequence of any DAF or additional amino acids at either or both ends of any DAF. The specification does not each what amino acids and from what species of DAF to be added to the first functional unit for the claimed protein.

With respect to the "polypeptides derived from Fc fragments of IgG4", there is no specific guidance as to which amino acids within the Fc fragments of IgG4 from which species to be modified by substitution, deletion, addition and/or combination thereof such that the derivatives maintain structure and function.

With respect to protein having an amino acid sequence that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23, the phrase "having an amino acid sequence" encompasses full-length as well as fragment thereof that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23.

The specification does not teach which amino acids with the full-length sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 to be modified by substitution, deletions, addition, or combination thereof such the protein having at least 5% difference still inhibit complement activity in a human subject, let alone any and all mammalian subjects, i.e., whale, pig, dog, cat, etc.

The protein of SEQ ID NO: 13 is 996 amino acids in length. A 5% difference is equivalent to 49 amino acids difference. Likewise, the protein of SEQ ID NO: 15 is 1446 amino acids in length. A 5% difference is equivalent to 72 amino acids difference. The specification provides no specific guidance as to where and what amino acids to be substituted, deleted, added, or combination thereof and in vivo working example to enable one of skill in the art to make and use the claimed protein for inhibiting complement activity in all mammals as broadly as claimed.

For example, Seffernick et al (J Bacteriol 183 (8): 2405-10, April 2001; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; DISCUSSION section on page 2409).

Chica et al. (Curr Opin Biotechnol 16(4):378-84, August 2005; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein be diminished with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Further, a method of inhibiting complement activity for treating diseases in mammal such as human in the absence of working example is unpredictable. For examples, while soluble DAF fused to IgG chimeric protein was effective in vitro, it efficacy was marginal in vivo, particularly in other species.

For example, Song et al (of record, J Clin Investigation 111(12): 1875-1885, June 2003; PTO 892) teach complement regulator from one species may not work in another species. For example, human CD59 and soluble human DAF are poor inhibitors of rodent complement relative to their activity against human complement with the exception of human DAF activity against the rat alternative pathway of activation (see page 1882, right col., in particular). As such, it is unclear which unspecified soluble fusion protein having at least 5% difference, i.e., up to 72 amino acids difference still inhibit complement activity in any and all mammalian subjects, i.e., whale, pig, human, etc for treating any disorder associated with complement activation.

For example, US2006/024066 application (newly cited, PTO 892) teaches it has been shown that human and rodent DAFs are not species specific in their complement inhibiting activities. However, administration of foreign complement regulator results in a prompt immune response in the recipient,

limiting its function to just a few days. This has restricted the ability to test human C regulators, such as sCR1, in chronic disease model in rodents, see paragraph [0011], in particular.

As such, one cannot extrapolate the teachings of the specification to the scope of the claims because the method claims are drawn to inhibiting any mammal by administering unspecified protein having at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23. However, the specification discloses just human DAF (CD55) consisting of CCPs 2-4 of human DAF fused to CCPs 8-10 of human Complement Receptor 1 (CR1), CCPs 15-17 of human CR1, the Fc fragment of IgG4 wherein the Fc fragment consisting of a hinge, CH2 and CH3 domain, or a lipid tail via a spacer of at least 200 amino acids in length.

Reasonable correlation must exist between the scope of the claims and the scope of enablement set forth.

Accordingly, it would require undue experimentation to make and use the claimed protein within the metes and bounds of the claims that would be reasonably expected to have the desired effect in any and all mammals.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed December 6, 2010 have been fully considered but are not found persuasive.

Applicants' position is that claim has been amended to recite that the first functional unit comprises at least CCPs 2, 3 and 4 of DAF. Claim 1 has also been amended to recite that the second

functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from IgG4, and a lipid tail. The specification of the application also includes working examples that demonstrate hybrid and chimeric proteins having the amino acid sequences SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23.

Although, the specification of the application does not provide working examples showing proteins having amino acid sequences other than those having SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23, the specification does provide guidance and direction such that a skilled artisan at the time of the invention would have been able to produce such proteins with an expectation of success without undue experimentation.

In response, although claim has been amended, claim1 still encompasses any protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of any DAF; a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of any Complement Receptor 1 (CR1), CCPs 15-17 of any CR1, any polypeptides derived from Fc fragments of IgG4, and a lipid tail.

The specification discloses just human DAF and human Complement Receptor 1 (CR1). Furthermore, the term "comprises" is open ended. It extends the DAF functional unit to include the full-length sequence of any DAF or any additional amino acids at either or both ends of any DAF. The specification does not each what amino acids and from what species of DAF to be added to the first functional unit for the claimed protein.

With respect to the "polypeptides derived from Fc fragments of IgG4", there is no specific guidance as to which amino acids within the Fc fragments of IgG4 from which species to be modified by

substitution, deletion, addition and/or combination thereof such that the derivatives of the unspecified Fc fragments still maintain structure and function. The specification discloses hybrid protein that comprises the Fc fragment of IgG4 which includes the hinge, CH2 and CH3 domains, see page 16. The claim as amended includes multiple polypeptides derived from multiple Fc fragments of any IgG4. There is no specific guidance and working example as to which amino acids within the Fc fragments of IgG4 from which species to be modified by substitution, deletion, addition and/or combination thereof such that the derivatives maintain structure and function. While the specification teaches assays to determine the functional characterization of the proteins, screening is not a method of how to make. The amino acid sequence or nucleic acid sequence encoding the claimed protein is required for making and using such protein.

With respect to protein having an amino acid sequence that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23, the phrase "having an amino acid sequence" encompasses full-length as well as fragment thereof that is that least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23.

The specification does not teach which amino acids with the full-length sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 to be modified by substitution, deletions, addition, or combination thereof such the protein having at least 5% difference still inhibit complement activity in any and all mammalian subjects, i.e., whale, pig, human, etc.

The protein of SEQ ID NO: 13 is 996 amino acids in length. A 5% difference is equivalent to 49 amino acids difference. Likewise, the protein of SEQ ID NO: 15 is 1446 amino acids in length. A 5% difference is equivalent to 72 amino acids difference. The protein of SEQ ID NO: 771 amino acids in length while SEQ ID NO: 23 is 802 amino acids in length. The specification provides no specific

guidance as where and what amino acids within any of the SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 to be substitute, deleted, added or combination thereof to enable one of skill in the art to make and use the claimed protein for inhibiting complement activity in all mammals as broadly as claimed. Further, there is no in vivo working example of such modified protein inhibits complement activity in human, let alone any and all mammals. It is known in the art that even a single amino acid difference, the protein has different function. In addition, one skilled in the art would expect any tolerance to modification for a given protein be diminished with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

For example, Seffernick et al (J Bacteriol 183 (8): 2405-10, April 2001; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; DISCUSSION section on page 2409).

Further, a method of inhibiting complement activity for treating diseases in mammal such as human in the absence of working example is unpredictable. For examples, while soluble DAF fused to IgG chimeric protein was effective in vitro, it efficacy was marginal in vivo, particularly in other species.

For example, Song et al (of record, J Clin Investigation 111(12): 1875-1885, June 2003; PTO 892) teach complement regulator from one species may not work in another species. For example, human CD59 and soluble human DAF are poor inhibitors of rodent complement relative to their activity against human complement with the exception of human DAF activity against the rat alternative pathway of activation (see page 1882, right col., in particular).

As another example, US2006/024066 application (newly cited, PTO 892) teaches it has been shown that human and rodent DAFs are not species specific in their complement inhibiting activities. However, administration of foreign complement regulator results in a prompt immune response in the

recipient, limiting its function to just a few days. This has restricted the ability to test human C regulators, such as sCR1, in chronic disease model in rodents, see paragraph [0011], in particular.

As such, it is unpredictable which unspecified soluble fusion protein having an amino acid sequence that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 still inhibit complement activity in human, let alone any and all mammalian subjects, i.e., whale, pig, dog, cat, etc for treating any disorder associated with complement activation. Thus undue experimentation would have required to practice the claimed protein. For these reasons, the rejection is maintained.

Claims 1-2, 5, 7, 12, 14-15, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any protein as set forth in claims 1-2, 5, 7 and 12 and a method of inhibiting complement activity by administering an effective amount of protein to any and all mammal, any mammal such as human, the protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23 or a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Claims 1 and 5 encompass any protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of any DAF; a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, spacer such as substantially all of the amino acids of CCPs4-7 of any CR1 or

substantially all of the amino acids of CCPs 11-14 of any CR1, attached to the first functional unit; and a second functional unit attached to said spacer sequence, such as CCPs 8-10 of any Complement Receptor 1 (CR1), CCPs 15-17 of any CR1, any polypeptides derived from Fc fragments of IgG4, or a lipid tail.

Claim 2 encompasses any protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of any DAF; a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of any Complement Receptor 1 (CR1), CCPs 15-17 of any CR1, any polypeptides derived from Fc fragments of IgG4, and a lipid tail and further comprising a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties attached to the second function domain, and a third functional unit attached to the second spacer, wherein the third functional unit is any polypeptides derived from Fc fragments of IgG4, or a lipid tail.

Claim 7 encompasses any protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of any DAF; a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of any Complement Receptor 1 (CR1), CCPs 15-17 of any CR1, any polypeptides derived from Fc fragments of IgG4, and a lipid tail and further comprising a second spacer comprising substantially all of the amino acids of CCPs 4-5 of CR1, and a third functional unit selected from the group consisting of CCPs 8-10 of CR1, CCPs 1-4 of MCP, and polypeptides derived from IgG4 Fc fragments of IgG4.

Claim 12 encompasses any protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Claim 14 encompasses a method of inhibiting complement activity comprising administering an effective amount of a protein to any and all mammal the protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Claim 15 encompasses a method of inhibiting complement activity comprising administering an effective amount of a protein to a human the protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Claims 19 and 20 encompass a method of inhibiting complement activity comprising administering an effective amount of a protein to any and all mammal the protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23.

At the time of filing, the specification discloses just human DAF (CD55) and human CR1 (CD35). The specification discloses chimeric protein comprising a first functional unit of a first complement regulatory protein, wherein the first functional unit consisting of CCPs 2-4 of human DAF, a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of human Complement Receptor 1 (CR1), CCPs 15-17 of human CR1, the Fc fragment of IgG4 wherein the Fc fragment consisting of a hinge, CH2 and CH3 domain, and a lipid tail. The hybrid fusion protein comprises the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23.

With respect to claim 1, the term "comprises" is open ended. It extends the DAF functional unit to include the full-length sequence of any DAF or additional amino acids at either or both ends of any DAF. The specification does not describe what amino acids and from what species of DAF to be added to the first functional unit for the claimed protein.

With respect to the "polypeptides derived from Fc fragments of IgG4", the specification does not describe the structure of any multiple polypeptides derived from Fc fragments of IgG4 from which species, much less where and what amino acids of Fc fragment of IgG4 to be modified by substitution, deletion, addition and/or combination thereof such that the derivatives maintain structure and function. Thus the disclosure does not allow one of skill in the art to visualize or recognize the structure of such protein having any polypeptides derived from Fc fragments of IgG4.

With respect to protein having an amino acid sequence that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23, the phrase "having an amino acid sequence" encompasses full-length as well as any fragment thereof so long the sequence is at least 95 percent homologous to a protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23.

The specification does not teach which amino acids within the full-length sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 to be modified by substitution, deletions, addition, or combination thereof such the modified protein having at least 5% difference still inhibits complement activity in human, let alone any mammals such as whale, pig, dog, cat, etc.

The protein of SEQ ID NO: 13 is 996 amino acids in length. A 5% difference is equivalent to 49 amino acids difference. Likewise, the protein of SEQ ID NO: 15 is 1446 amino acids in length. A 5% difference is equivalent to 72 amino acids difference. The specification provides no specific guidance as to where and what amino acids to be substituted, deleted, added or a combination thereof and still inhibiting complement activity.

For example, Seffernick et al (J Bacteriol 183 (8): 2405-10, April 2001; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; DISCUSSION section on page 2409).

Chica et al. (Curr Opin Biotechnol 16(4):378-84, August 2005; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein be diminished with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Further, a method of inhibiting complement activity for treating diseases in mammal such as human in the absence of working example is unpredictable. While soluble DAF fused to IgG chimeric protein was effective in vitro, its efficacy was marginal in vivo, particularly in other species.

For example, Song et al (of record, J Clin Investigation 111(12): 1875-1885, June 2003; PTO 892) teach complement regulator from one species may not work in another species. For example, human CD59 and soluble human DAF are poor inhibitors of rodent complement relative to their activity against human complement with the exception of human DAF activity against the rat alternative pathway of activation (see page 1882, right col., in particular). As such, it is unclear which unspecified soluble fusion protein having at least 5% difference or up to 72 amino acids difference still inhibits complement activity in human, let alone any and all mammals, i.e., whale, pig, human, etc for treating any disorder associated with complement activation.

For example, US2006/024066 application (newly cited, PTO 892) teaches it has been shown that human and rodent DAFs are not species specific in their complement inhibiting activities. However, administration of foreign complement regulator results in a prompt immune response in the recipient, limiting its function to just a few days. This has restricted the ability to test human C regulators, such as sCR1, in chronic disease model in rodents, see paragraph [0011], in particular. Thus the disclosure does not allow one of skill in the art to visualize or recognize the structure of such protein having at least 95% homologous to a protein having the amino acid sequence of SEQ NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 as required to practice the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v. Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences.

Therefore, only isolated protein comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23, and a method of inhibiting complement activity comprising administering to a human, mouse or rat subject an effective amount of a protein comprising the amino acid sequence selected from the group consisting of SEQ ID

NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23 effective to inhibit complement activity, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicants' arguments filed December 6, 2010 have been fully considered but are not found persuasive.

Applicants' position is that claim has been amended to recite that the first functional unit comprises at least CCPs 2, 3 and 4 of DAF. Claim 1 has also been amended to recite that the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from IgG4, and a lipid tail. The specification of the application also includes working examples that demonstrate hybrid and chimeric proteins having the amino acid sequences SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23.

Although, the specification of the application does not provide working examples showing proteins having amino acid sequences other than those having SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23, the specification does provide guidance and direction such that a skilled artisan at the time of the invention would have been able to produce such proteins with an expectation of success without undue experimentation.

In response, although claim has been amended, claim1 still encompasses any protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of any DAF; a first spacer sequence of at least about 200 amino acids wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs

8-10 of any Complement Receptor 1 (CR1), CCPs 15-17 of any CR1, any polypeptides derived from Fc fragments of IgG4, and a lipid tail.

The specification discloses just human DAF and human Complement Receptor 1 (CR1). The term "comprises" is open ended. It extends the DAF functional unit to include the full-length sequence of any DAF or any additional amino acids at either or both ends of any DAF. The specification does not each what amino acids and from what species of DAF to be added to the first functional unit for the claimed protein.

With respect to the "polypeptides derived from Fc fragments of IgG4", there is no specific guidance as to which amino acids within which Fc fragments of IgG4 from which species to be modified by substitution, deletion, addition and/or combination thereof such that the derivatives of the unspecified Fc fragments still maintain structure and function. The specification discloses chimeric protein comprises the Fc fragment of IgG4 which consisting of the hinge, CH2 and CH3 domains, see page 16. The claim as amended includes multiple polypeptides derived from multiple Fc fragments of any IgG4. There is no specific guidance and working example as to which amino acids within the Fc fragments of IgG4 from which species to be modified by substitution, deletion, addition and/or combination thereof such that the derivatives maintain structure and function. Thus the disclosure does not allow one of skill in the art to visualize or recognize the structure of such hybrid protein having multiple polypeptides derived from Fc fragments of any IgG4. While the specification teaches assays to determine the functional characterization of the proteins, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

With respect to protein having an amino acid sequence that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23, the phrase "having an amino acid sequence" encompasses full-length as well as any fragment

thereof so long the protein is least 95 percent homologous to a protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23.

The specification does not describe where and what amino acids within the full-length sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 to be modified by substitution, deletions, addition, or combination thereof such that the modified protein having at least 5% difference still inhibits complement activity in human, let alone any and all mammalian subjects, i.e., whale, pig, dog, cat, etc. It is noted that the protein of SEQ ID NO: 13 is 996 amino acids in length. A 5% difference is equivalent to 49 amino acids difference. Likewise, the protein of SEQ ID NO: 15 is 1446 amino acids in length. A 5% difference is equivalent to 72 amino acids difference. The specification provides no specific guidance as where and what amino acid within any of the SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 to be substitute, deleted, added or combination thereof. Thus the disclosure does not allow one of skill in the art to visualize or recognize the structure of such protein having at least 95% homologous to a protein having the amino acid sequence of SEQ NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 as required to practice the claimed invention.

It is known in the art that even a single amino acid difference, the protein has different function. In addition, one skilled in the art would expect any tolerance to modification for a given protein be diminished with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

For example, Seffernick et al (J Bacteriol 183 (8): 2405-10, April 2001; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; DISCUSSION section on page 2409).

Further, a method of inhibiting complement activity for treating diseases in mammal such as human in the absence of working example is unpredictable. For example, Song et al (of record, J Clin

Investigation 111(12): 1875-1885, June 2003; PTO 892) teach complement regulator from one species may not work in another species. For example, human CD59 and soluble human DAF are poor inhibitors of rodent complement relative to their activity against human complement with the exception of human DAF activity against the rat alternative pathway of activation (see page 1882, right col., in particular).

As another example, US2006/024066 application (newly cited, PTO 892) teaches it has been shown that human and rodent DAFs are not species specific in their complement inhibiting activities. However, administration of foreign complement regulator results in a prompt immune response in the recipient, limiting its function to just a few days. This has restricted the ability to test human C regulators, such as sCR1, in chronic disease model in rodents, see paragraph [0011], in particular.

As such, it is unpredictable which unspecified soluble fusion protein having an amino acid sequence that is at least 95 percent homologous to a protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23 still inhibits complement activity in human, let alone any and all mammalian subjects, i.e., whale, pig, dog, cat, etc for treating any disorder associated with complement activation. As such, the functional definition (inhibiting complement activity in human as opposed to mouse or cat) cannot be correlated with the disclosed structure of protein having an amino acid sequence that is at least 95 percent homologous to protein to any protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 or SEQ ID NO: 23. For these reasons, the rejection is maintained.

New ground of objections and rejections are necessitated by the amendment filed December 6, 2010.

Claim 1 is objected to because of the following informality: “poly peptides” should be one word, i.e., "polypeptides".

Claim 7 is objected to because of the following informality: “compromising” should have been “comprising”.

The disclosure is objected because it fails to provide antecedent basis for the original claimed term "a first spacer sequence of at least about 200 amino acids".

Claim rejections under - 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

Claims 1-2, 5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is New Matter.**

The recitation of "polypeptides derived from Fc fragments of IgG4" in amended claims 1, 2 and 7 has no support in the specification and the claims as originally filed. The specification discloses just the Fc fragment consisting of the hinge, CH2 and CH3 domains of IgG4, see paragraph [0063]. The specification does not disclose any derivative from any Fc fragments of any IgG4 as a second functional unit and a third functional unit in the claimed protein such as multiple tandem Fc fragments in the claimed protein.

Claim 2 encompasses (a) a protein comprising CCPs2, 3 and 4 of DAF, a first spacer sequence of at least 200 amino acids that does not exhibit complement regulating properties, a second functional unit polypeptides derived from Fc fragments of IgG4, a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, and a third functional unit such as polypeptides derived from Fc fragments of IgG4, (b) a protein comprising CCPs2, 3 and 4 of DAF, a first spacer sequence of at least 200 amino acids that does not exhibit complement regulating properties, a second functional unit lipid tail, a second spacer sequence of at least about 200 amino acids that does not

exhibit complement regulating properties, and a third functional unit such as polypeptides derived from Fc fragments of IgG4; (c) a protein comprising CCPs2, 3 and 4 of DAF, a first spacer sequence of at least 200 amino acids that does not exhibit complement regulating properties, a second functional unit polypeptides derived from Fc fragments of IgG4, a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, and a third functional unit such as a lipid tail; (d) a protein comprising CCPs2, 3 and 4 of DAF, a first spacer sequence of at least 200 amino acids that does not exhibit complement regulating properties, a second functional unit such as a lipid tail, a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, and a third functional unit such as a lipid tail.

Neither the specification nor the claims as originally filed provides written support for a hybrid protein comprising CCPs 2-4 of DAF having tandem Fc of IgG4 or tandem lipid tails or combination of both such as lipid tail and Fc IgG4 or Fc of IgG4 and lipid tail. This is new matter. Note, amending claim 1 by deleting the phrase "polypeptides derived from Fc fragments of IgG4 and a lipid tail" and inserting "and" before "CCPs 15-17 of CR1" and replace "polypeptides derived from Fc fragments of IgG4" with "Fc of IgG4" in claims 2 and 7 would obviate this rejection.

Claim rejections under - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/08570 publication (of record, published March 30, 1995; PTO 892) in view of US Pat No 6,280,732 (newly cited, issued August 2001, PTO 892) and by Harris et al (of record, J Biol Chemistry 278(38): 36068-36076, September 2003; PTO 892) or Harris et al (newly cited, Clin Exp Immunol 129: 198-207, 2002; PTO 892).

The WO 95/08570 publication teaches a chimeric fusion protein DAF-MCP comprising a first functional unit of a first complement regulatory protein such as DAF comprising the first four short consensus repeats CCPs 1, 2, 3 and 4 of DAF (see page 11, lines 28-35 through page 12, lines 1-6, in particular), a first spacer sequence that does not exhibit complement regulating activity ranging from 0 to 1500 amino acids long which included the claimed at least about 200 amino acids (see page 12, lines 12-20, in particular) and a second functional unit attached to said spacer sequence such as CCPs 1-4 of membrane cofactor protein (MCP) (see abstract, page 29-30, claims 1-8, in particular). The term "comprises" is open-ended. It expands the claimed CCPs 2, 3 and 4 of DAF to include the CCP1 of the reference DAF. The term "at least about" includes about 200 amino acids or more. The WO 95/08570 publication also teaches a method of inhibiting complement activity by administering an effective amount of the reference chimeric fusion protein to a mammal such as a patient for reducing inflammation characterized by excessive complement activation (see claims 18-19 of the reference, pain particular).

WO 95/08570 publication does not teach the second functional unit is polypeptides derived from Fc fragments of IgG4 instead of CCPs 1-4 of MCP.

However, The '732 patent teach the simplest and most straightforward immunoadhesin design combined the binding region(s) of the `adhesin` protein (in this case AL-1 or REK-7) with the hinge and Fc regions of an immunoglobulin heavy chain. Ordinarily, when preparing chimeras of the present invention, nucleic acid encoding the extracellular domain or a fragment thereof of AL-1 or REK-7 will be fused C-terminally to nucleic acid encoding the N-terminus of an immunoglobulin constant domain sequence, however N-terminal fusions are also possible. Typically, in such fusions the encoded chimeric polypeptide will retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Fusions are also made to the C-terminus of the Fc portion of a constant domain, or immediately N-terminal to the CH1 of the heavy chain or the corresponding region of the light chain. The precise site at which the fusion is made is not critical; particular sites are well known and may be selected in order to optimize the biological activity, secretion or binding characteristics of the AL-1 or REK-7 receptor-immunoglobulin chimeras, see col. 25, in particular. The '732 patent teaches although IgG1, IgG2 and IgG4 all have in vivo half-lives of 21 days, their relative potencies at activating the complement system are different. For example, IgG4 does not activate complement, see entire document, col. 26, lines 32-38, in particular).

Harris et al teaches various chimeric fusion protein such as DAF4-IDG75-IgG4 comprising a first complement regulatory protein such as all amino-terminal 1-4 short consensus repeat (SCRs) from human DAF fused a first spacer sequence such as 75 amino acids of IGF sequence and a second functional unit derived from Fc of IgG4 such as the Fc of human IgG4 that includes the hinge, CH2 and CH3 domains of IgG4, see page 36070, results, page 36071, right col., page 36072, Table 1(a), in particular). The antibody Fc domain markedly improves the in vivo half life of DAF fusion protein (see abstract, page 36070, right col., in particular). Harris et al further teach that short spacing between DAF and the

antibody IgG4 Fc resulted in steric hindrance in binding of DAF to its large substrate but a long spacer sequence such as 75 amino acids between DAF and the Fc hinge would partially restored function of DAF (see abstract, page 36069, left col., in particular).

Harris et al (Clin Exp Immunol 129: 198-207, 2002; PTO 892) teach coupling of decay accelerating factor (DAF, also known as CD55) or CD59 to Fc of IgG1 or CD59-spacer-Ig (see entire document, page 202, in particular). Harris et al teach Ig Fusion of DAF or CD59 without spacer reduced the Complement inhibitory capacity of DAF by twelve fold due to steric hindrance (see page 205, left col., in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the MCP in the fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and MCP of the WO 95/08570 publication for the Fc domain of human IgG4 as taught by the '732 patent to form a new fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and Fc of IgG4 to improve the serum half-life of the fusion protein in addition to reduce the steric hindrance as taught by Harris et al (Clin Exp Immunol 129: 198-207, 2002). In this case, simple substitution of one known element for another would obtain predictable results.

In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse the CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids that lacks complement regulating activity of the WO 95/08570 publication to the human IgG4 Fc to improve the half life of the fusion protein.

One of ordinary skill in the art would have been motivated with the expectation of success to lengthen the spacer sequence between DAF and second functional unit such as Fc to eliminate steric hindrance because spacer sequence of 75 amino acids partially restored the function of DAF as taught by Harris et al (see J Biol Chemistry 278(38): 36068-36076, September 2003, abstract, page 36069, left col.,

in particular) while no spacer sequence reduces the function of DAF by twelve fold as taught by Harris et al (see Clin Exp Immunol 129: 198-207, 2002; page 205, left col., in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to substitute MCP for the Fc of IgG4 in view of Harris et al because Harris et al teach the Fc of IgG4 extends the in vivo half life of the soluble DAF (see abstract, page 36070, right col., in particular). Furthermore, the Fc of IgG4 does not have any complement activity as evidentiary reference Smith et al teach the Fc of IgG4 normally devoid of complement activity (see abstract, in particular).

One having ordinary skill in the art would have been motivated to increase the length of the spacer between DAF, second and third functional domains of complement regulatory protein because short spacer sequence caused steric hindrance and longer spacer sequence restore activity of the complement regulatory functional subunits as taught by Harris et al (see abstract, page 36069, left col., in particular) or Harris et al (Clin Exp Immunol 129: 198-207, 2002; PTO 892, see page 205, left col., in particular).

It is within of one of ordinary skill in the art to lengthen any spacer sequence to remove any steric hindrance by mimicking the natural structure of DAF which has lengthy CCPs to reduce steric hindrance as taught by Harris et al (Clin Exp Immunol 129: 198-207, 2002; PTO 892, see page 205, left col., in particular). As evidence in the specification, "such spacer is a polypeptide that is greater than 200 amino acids in length, preferably greater than 250 amino acids in length, see page 15, lines 1-3.

Applicants' arguments filed December 6, 2010 have been fully considered but are not found persuasive.

Applicants' position is that Claim 1 has been amended to recite a protein comprising a second functional unit attached to the spacer sequence wherein the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from Fc fragments of IgG4, and a lipid tail.

Claim 1 is not obvious in view of is the '570 publication in view of Harris et al. as evidenced by Smith et al. because Harris et al. teaches away from linking a DAF functional unit to the Fc domains of human IgG4 using the spacer sequence of the '570 publication.

The '570 publication teaches a chimeric protein having a first functional unit of CCPs 2-4 of DAF and a second functional unit of CCPs 1-4 of MCP. The '570 patent does not teach a chimeric protein having a second functional unit attached to the spacer sequence wherein the second functional unit is comprised of polypeptides derived from IgG4.

Harris et al. teach fusion protein prodrugs comprising four human DAF short consensus repeats linked to IgG4 Fc. However, Harris et al. teach that the fusion protein prodrugs have a markedly decreased complement inhibitory activity when compared with the parent regulator in vitro (Abstract). Due to the stated inhibitory activity, Harris et al. teach that DAF and IgG4 Fc must be linked by a 75 amino acid sequence of the Interglobular Domain (IGD) of aggrecan which contains specific cleavage sites for metalloproteinases and/or aggrecanases (Fig. 2B, p. 36069, left col. and p. 36070, right col.) Harris et al. indicates that the cleavage sites allow for cleavage of the IgG4 functional unit of the prodrug from DAF, in order to release the active complement regulator (Abstract). Smith et al. merely discuss that the Fc region of IgG4 normally is devoid of complement activity.

According to the teachings Harris et al., a DAF-IgG4 fusion protein that does not include a cleavable linker would retain the IgG4 Fc functional unit and would have markedly decreased complement inhibitory activity when compared with the parent regulator (e.g., DAF) in vitro. Thus, Harris et al. teaches away from the use of a spacer amino acid sequence that does not include specific cleavage sites allowing for the release of the active complement regulator in a DAF-IgG4 Fc fusion protein spacer sequence in order to avoid decreased complement inhibitory activity.

The spacer sequence of the '570 publication does not include specific cleavage sites allowing for the release of the active complement regulator. Therefore, a combination of the '570 publication and

Harris et al. would teach that a simple substitution of IgG4 Fc for MCP in the fusion protein of the '570 publication would have a markedly decreased complement inhibitory activity when compared with the parent regulator. Therefore, one skilled in the relevant art would not look to combine the spacer sequence and DAF functional unit of the '570 publication with the IgG4 Fc functional unit of Harris et al. because Harris et al. teaches away from such a combination. Accordingly, it would not have been obvious to one of ordinary skill in the art at the time of the invention to link a DAF functional unit to the Fc domains of human IgG4 using the spacer sequence of the '570 publication because Harris et al. teach away from such a combination.

In response to applicants' argument that Harris et al. teaches away from the claimed protein by using a spacer amino acid sequence that include specific cleavage sites allowing for the release of the active complement regulator in a DAF-IgG4 Fc fusion protein spacer sequence in order to avoid decreased complement inhibitory activity, the combined teachings of the WO 95/08570 publication in view of the '732 patent would produce the claimed DAF-long spacer-IgG4 Fc that does not inhibit the interaction between DAF and its target due to the long spacer of up to 1000 amino acids as taught by the WO 95/08570 publication. The Fc fragment of IgG4 from '732 patent does not include cleavage sites.

The motivation as to why one would include a long spacer between DAF and second functional unit such as Fc is provided by Harris et al. Harris et al teach that short spacing between DAF and the antibody IgG4 Fc resulted in steric hindrance in binding of DAF to its large substrate but a long spacer sequence between DAF and the Fc hinge would partially restored function of DAF (see abstract, page 36069, left col., in particular). As expected, the spacer amino acid sequence of the WO 95/08570 publication is sufficient long, i.e., up to 1000 amino acid residues in length and would not hinder the binding of DAF to its large substrate.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/08570 publication (of record, published March 30, 1995; PTO 892) in view of Harris et al (newly cited, Biochemcial Society Transactions 30(6): 1019-1025, 2002; PTO 892).

The WO 95/08570 publication teaches a chimeric fusion protein DAF-MCP comprising a first functional unit of a first complement regulatory protein such as DAF comprising the first four short consensus repeats CCPs 1, 2, 3 and 4 of DAF (see page 11, lines 28-35 through page 12, lines 1-6, in particular), a first spacer sequence that does not exhibit complement regulating activity ranging from 0 to 1500 amino acids long which included the claimed at least about 200 amino acids (see page 12, lines 12-20, in particular) and a second functional unit attached to said spacer sequence such as CCPs 1-4 of membrane cofactor protein (MCP) (see abstract, page 29-30, claims 1-8, in particular). The term "comprises" is open-ended. It expands the claimed CCPs 2, 3 and 4 of DAF to include the CCP1 of the reference DAF. The term "at least about" includes about 200 amino acids or more. The WO 95/08570 publication also teaches a method of inhibiting complement activity by administering an effective amount of the reference chimeric fusion protein to a mammal such as a patient for reducing inflammation characterized by excessive complement activation (see claims 18-19 of the reference, pain particular).

WO 95/08570 publication does not teach the second functional unit is lipid tail instead of CCPs 1-4 of MCP.

Harris et al teach various complement inhibitors such as DAF (also known as CD55), C receptor 1 (also known as CR1 or CD35) inhibit the convertase enzymes (see page 1020, left col., in particular). Harris et al teach truncated form of sCR1 comprising the three N-terminal SCRs have been linked to an "addressin" such a lipolic acyl chain (lipid tail) that myristate to target the soluble CR1 to enhance membrane targeting which proves beneficial in various models of disease including arthritis and ischemia perfusion (see page 1023, left col., in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the MCP in the fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and MCP of the WO 95/08570 publication for the lipid tail that target the DAF to membrane as taught by Haris et al (Biochemical Society Transactions 30(6): 1019-1025, 2002) to form a new fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and a lipid tail. In this case, simple substitution of one known element for another would obtain predictable results.

In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse the CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids of the WO 95/08570 publication to the lipid tail of Haris et al for targeting the soluble DAF to membrane. In this case, combining prior art elements according known methods would yield predictable results. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to substitute MCP for the lipid tail in view of Harris et al because the lipolic acyl chain (lipid tail) enhance membrane targeting of DAF which proves beneficial in various models of disease including arthritis and ischemia perfusion as taught by Harris et al (see page 1023, left col., in particular).

One having ordinary skill in the art would have been motivated to increase the length of the spacer between DAF and lipid tail because short spacer sequence caused steric hindrance and longer spacer sequence restore activity of the complement regulatory functional subunits as taught by Harris et al (see abstract, page 36069, left col., in particular). It is within of one of ordinary skill in the art to lengthen any spacer sequence to remove any steric hindrance. The term "comprises" extends the DAF to include CCP1, 2, 3 and 4 of DAF. The term "at least about" includes spacer is about 200 or more amino

acids. As evidence in the specification, "such spacer is a polypeptide that is greater than 200 amino acids in length, preferably greater than 250 amino acids in length, see page 15, lines 1-3.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained

from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644